REMARKS

Claims 59-87 are currently pending in the subject application. Applicant has cancelled claims 59-87 herein without prejudice or disclaimer to applicant's right to pursue the subject matter of these claims in the future. In addition, applicant has added new claims 88-101.

Support for new claim 88 can be found in the specification as originally filed at, *inter alia*, page 4, lines 3-5; page 5, lines 19-22; and page 6, line 29 to page 7, line 1. Support for new claims 89 and 95 can be found in the specification as originally filed at, *inter alia*, page 5, lines 19-22 and page 7, line 16. Support for new claims 90 and 96 can be found in the specification as originally filed at, *inter alia*, page 5, lines 19-22 and page 7, line 17. Support for new claims 91 and 97 can be found in the specification as originally filed at, *inter alia*, page 5, lines 19-22 and page 7, line 18. Support for new claims 92 and 98 can be found in the specification as originally filed at, *inter alia*, page 5, lines 19-22 and page 7, line 19. Support for new claims 93, 99, and 101 can be found in the specification as originally filed at, *inter alia*, page 6, line 35 to page 7, line 1. Support for new claim 94 can be found in the specification as originally filed at, *inter alia*, page 8, line 1. Support for new claim 100 can be found in the specification as originally filed at, *inter alia*, page 4, lines 3-5 and lines 25-28; page 5, lines 19-22; page 6, line 29 to page 7, line 1; and page 8, line 1. Applicant maintains that the amendments to the claims raise no issue of new matter. Accordingly, applicant respectfully requests entry of this Amendment.

Rejection Under 35 U.S.C. §102(b)

In the August 25, 2006 Office Action the Examiner rejected claims 59-61, 63, 66-70, 72-76, 78-82 and 84-87 under 35 U.S.C. §102(b) as allegedly anticipated by Karim et al. (Clinical Pharmacology and

Therapy, 5:862-869, 1973). The Examiner asserted that Karim et al. teach a liquid composition comprising oxandrolone, ethanol and water, and that the oxandrolone is present in an amount of 10mg.

In response, applicant has rewritten the claims for clarity and respectfully traverses the Examiner's rejection in so far as it applies to the new claims and also the rejections' application to the previously pending claims. Applicant notes that Karim et al. discuss a composition comprising ^{14}C-oxandrolone. Applicant notes that ^{14}C-oxandrolone comprises the radioactive isotope carbon-14. As such, it has a different subatomic structure than oxandrolone, and is a different entity. In addition, applicants note that Karim et al. do not teach a solid dosage form comprising 10 mg of oxandrolone per unit dosage form as recited in the new claims.

Accordingly, applicant maintains that Karim et al. do not teach all elements of applicant's claimed invention (as recited in previously pending claims or currently pending claims) and respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 59-87 under 35 U.S.C. §103(a) as allegedly obvious over Metcalf. Specifically, the Examiner alleged that Metcalf teaches a method of using oxandrolone for nitrogen retention wherein the daily amounts of oxandrolone are from 5 mg, 10 mg, 20 mg, and up to 150 mg. The Examiner also alleged that oxandrolone was taken as a single dose daily, referring to page 60 of Metcalf, and that Metcalf teaches that the optimal dosage is 25 mg or 30 mg a day.

In response, applicant respectfully traverses the Examiner's rejection.

Applicant notes that, in the August 25, 2006 Office Action, the Examiner did not address the arguments made in applicant's last-filed response to the §103(a) rejection over Metcalf, i.e. the Amendment filed May 12, 2006. Applicant herein reiterates all no-addressed arguments and respectfully requests full consideration of all of applicants' reasons in support of patentability.

Metcalf Does Not Suggest All Elements of the Claimed Invention

Applicant maintains that the Examiner has not shown that Metcalf suggests a pharmaceutical composition containing 10 mg of oxandrolone in a single solid unit dosage form. In fact, as explained in further detail below, in 1965, the only approved oxandrolone formulation was ANAVAR®, which was available only in 2.5 mg unit doses. Nothing in Metcalf suggests a 10 mg oxandrolone solid dosage form.

Metcalf refers to a total combined daily "dosage" but does not indicate that the "dosage" was a single solid dosage unit.

Implicitly acknowledging the fact that this claim element is missing from the Metcalf reference, the Examiner has on this record alleged 1) that applicant has not provided "clear and direct" evidence that Metcalf used the dosage form on the market at that time, and 2) that Metcalf does not state whether the daily dosage is composed of multiple pills. However, applicants respectfully submit that the burden is not on applicant to prove a negative, i.e. to prove a claim element missing from a prior art reference. Rather, the initial burden of factual support for an obviousness rejection rests on the Examiner. This burden has not been satisfied.

Nevertheless, applicant does provide "clear and direct" evidence that Metcalf does not support the Examiner's assertions. Notably, the Examiner explicitly acknowledged that Metcalf does not state whether multiple pills or a single dosage was administered. This

uncontested fact, by itself, necessitates withdrawal of the rejection for failing to establish every element of the claims, i.e. that the oxandrolone is in the form of a single unit dose with the claimed dosage of 10 mg of oxandrolone in a single dose unit.

Moreover, applicant maintains that a person skilled in the art would necessarily understand Metcalf as using multiple pills to achieve the daily dosage level. The disclosure of Metcalf specifically states that its research was financially supported by G.D. Searle and that the oxandrolone used was produced and provided by G.D. Searle. The footnote on page 59 of Metcalf states: "This investigation was supported by a grant from G.D. Searle and Co." The footnote also discloses that the oxandrolone used was "[s]ynthesized by Dr. Rapheal Pappo, Division of Chemical Research, G.D. Searle and Co." On page 66, Metcalf further states: "We are grateful for the support of these studies from G.D. Searle and Company …."

The only oxandrolone formulation available to the public in 1964 from G.D. Searle and Co. was ANAVAR® tablets, each containing 2.5 mg of oxandrolone. See pages 1 and 15 of the Physician's Product Brochure No. 43 for ANAVAR® Brand of Oxandrolone, which the applicant previous submitted in the Fourth Supplemental Information Disclosure Statement dated October 11, 2005.

It is notable that Metcalf only administered dosages which are multiples of 2.5 mg, i.e. 2.5, 5, 10, 20, 40, 80 and 150 mg/day, since oxandrolone was only available at the time of the reference in the form of 2.5 mg tablets.

In summary, the Examiner has not provided any factual support for the rejection of a claim to a solid dosage form having 10 mg of oxandrolone. Instead, the August 25, 2006 Office Action repeats the rejection without addressing this deficiency in the rejection, which deficiency applicant has clearly pointed out on the record.

This is improper.

In view of the remarks above and the Examiner's failure to establish otherwise with evidence, it is apparent that Metcalf does not teach or suggest a composition comprising 10mg of oxandrolone per unit dose as set forth in applicant's current claims. Therefore, there is no justifiable reason to continue to delay allowance of this application.

No Selection

Applicant also maintains that the genus of ranges disclosed in Metcalf does not teach selection of the species recited in applicant's claim, i.e. of 10 mg. Applicant notes that "the mere fact that a prior art genus contains a small number of members does not create a per se rule of obviousness. Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215", (MPEP §2144.08 (II)(A)(4)(a)). Moreover, "lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus. In re Albrecht, 514 F.2d 1389, 1392, 1395-96, 185 USPQ 585, 587, 590 (CCPA 1975)", (MPEP §2144.08 (II)(A)(4)(d)). Accordingly, applicant maintains that Metcalf fails to teach selection of unit doses of 10 mg of oxandrolone.

Metcalf Teaches Away From the Claimed Invention

Applicant also maintains that Metcalf teaches away from the claimed invention because it discloses that the nitrogen retention for patients taking oxandrolone is at best ambiguous and, actually teaches that it is <u>less</u> <u>effective</u> in patients taking the presently claimed dosage.

As known in the art, nitrogen retention is a measure of therapeutic success in patients suffering from muscle wasting, myopathy, and low body weight from chronic human immunodeficiency virus type-1 infection. Thus, while the Examiner correctly points out that

Metcalf discloses *total combined* oxandrolone doses from 5, 10, 20 and up to 150 milligrams per day (Office Action at 2), Metcalf expressly acknowledges that the effects of such dosages were completely not understood. See, e.g. page 60 of Metcalf which states that the researchers were "uncertain which of the dose responses to include in the final analysis because of the variable response at low dose levels."

Rather than suggesting applicant's claimed 10 mg solid dosage form, Metcalf actually teaches away from the claimed invention by clearly teaching that daily dosages under the "optimum" dosage level of 25 milligrams did not help patients retain nitrogen. Clearly, Metcalf is teaching that 10 mg oxandrolone treatment is ineffective. An obviousness rejection based on a reference teaching against making applicant's claimed invention is improper.

Secondary Considerations

Applicant notes that, to his knowledge, as of the priority date of the present application, no composition as recited in the amended claims had been produced or made available despite G.D. Searle and Co. having been selling 2.5 mg oxandrolone tablets (ANAVAR®) since 1964. Metcalf had been published in 1965. Yet, no one had made or disclosed a solid dosage form of 10 mg oxandrolone and no one but the Examiner after benefit of applicant's disclosure had considered doing so obvious.

Conclusion

In view of the foregoing, there is no justifiable reason to continue to delay allowance of this application. Withdrawal of Examiner's rejections and allowance of the currently pending claims are respectfully requested.

Supplemental Information Disclosure Statement

In accordance with his duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the following references listed on the attached Form PTO-1449 (**Exhibit A**). References 1-8 are U.S. Patents. No copy of this reference is attached hereto, as permitted under 37 C.F.R. §1.98(a)(2)(ii). Copies of references 9-57 are attached hereto as **Exhibits 1-46**, respectively.

1. U.S. Patent No. 4,112,123, issued 9/5/1978, Roberts et al.;
2. U.S. Patent No. 5,021,404, issued 06/04/1991, Folkman et al.;
3. U.S. Patent No. 5,726,146, issued 3/10/1998, Almada et al.;
4. U.S. Patent No. 6,011,023, issued 1/4/2000, Clark et al.;
5. U.S. Patent No. 4,039,668, issued 8/2/1977, Fuchs et al.;
6. U.S. Patent No. 4,376,733, issued 3/15/1985, Frimer;
7. U.S. Patent No. 4,914,106, issued 4/3/1990, Shibata et al.;
8. U.S. Patent No. 5,096,916, issued 3/17/1992, Skupin et al.;
9. Aulick and Wilmore, (May 1979), "Increased Peripheral Amino Acid Release Following Burn Injury," Surgery, Vol. 85, pp. 560-565;
10. Bessey et al., (1989), "Post Traumatic Skeletal Muscle Proteolysis: The Role of the Hormonal Environment," World J. Surg., Vol. 13, pp. 465-470;
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22. Herndon et al., (October 1988), "Effect of Propranolol Administration on Hemodynamic and Metabolic Response of Burned Pediatric Patients," Ann. Surg., Vol. 208, pp. 484-492;
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24. Hickson et al., (1995), "Glutamine Prevents Down-Regulation of Myosin Heavy Chain Synthesis and Muscle Atrophy From Glucocorticoids," Am. J. Physiol., Vol. 268, pp. 730-734;
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26. Jeevanadam et al., (May 1992), "Decreased Growth Hormone Levels in the Catabolic Phase of Severe Injury," Surgery, Vol. 111, pp. 495-502;
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Management of the Critically Ill, Plenum Medical Books Co., New York, Wilmore Ed., pp. 171-233;

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, except the enclosed $180.00 fee for filing the Supplemental Information Disclosure Statement and $60.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fees are deemed necessary, authorization is hereby given to charge the amount of such fees to Deposit Account No. 03-3125.

Respectfully submitted,

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